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NEWS 1		Web Page for STN Seminar Schedule - N. America
NEWS 2	JUL 02	LMEDLINE coverage updated
NEWS 3	JUL 02	SCISEARCH enhanced with complete author names
NEWS 4	JUL 02	CHEMCATS accession numbers revised
NEWS 5	JUL 02	CA/CAplus enhanced with utility model patents from China
NEWS 6	JUL 16	CAplus enhanced with French and German abstracts
NEWS 7	JUL 18	CA/CAplus patent coverage enhanced
NEWS 8	JUL 26	USPATFULL/USPAT2 enhanced with IPC reclassification
NEWS 9	JUL 30	USGENE now available on STN
NEWS 10	AUG 06	CAS REGISTRY enhanced with new experimental property tags
NEWS 11	AUG 06	FSTA enhanced with new thesaurus edition
NEWS 12	AUG 13	CA/CAplus enhanced with additional kind codes for granted patents
NEWS 13	AUG 20	CA/CAplus enhanced with CAS indexing in pre-1907 records
NEWS 14	AUG 27	Full-text patent databases enhanced with predefined patent family display formats from INPADOCDB
NEWS 15	AUG 27	USPATOLD now available on STN
NEWS 16	AUG 28	CAS REGISTRY enhanced with additional experimental spectral property data
NEWS 17	SEP 07	STN AnaVist, Version 2.0, now available with Derwent World Patents Index
NEWS 18	SEP 13	FORIS renamed to SOFIS
NEWS 19	SEP 13	INPADOCDB enhanced with monthly SDI frequency
NEWS 20	SEP 17	CA/CAplus enhanced with printed CA page images from 1967-1998
NEWS 21	SEP 17	CAplus coverage extended to include traditional medicine patents
NEWS 22	SEP 24	EMBASE, EMBAL, and LEMBASE reloaded with enhancements
NEWS 23	OCT 02	CA/CAplus enhanced with pre-1907 records from Chemisches Zentralblatt
NEWS 24	OCT 19	BEILSTEIN updated with new compounds

NEWS EXPRESS 19 SEPTEMBER 2007: CURRENT WINDOWS VERSION IS V8.2, CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP), AND CURRENT DISCOVER FILE IS DATED 19 SEPTEMBER 2007.

NEWS HOURS	STN Operating Hours Plus Help Desk Availability
NEWS LOGIN	Welcome Banner and News Items
NEWS IPC8	For general information regarding STN implementation of IPC 8

Enter NEWS followed by the item number or name to see news on that specific topic.

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* * * * * * * * * * * * * * * * STN  Columbus  * * * * * * * * * * * * * * * *

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that are available.  If you have requested multiple files, you can
specify a corrected file name or you can enter "IGNORE" to continue
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COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                         ENTRY    SESSION
FULL ESTIMATED COST                                       0.21       0.21

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=> ((tissue factor) or  thromboplastin) and thrombomodulin and coagulation
L1           0 FILE AGRICOLA
L2          63 FILE BIOTECHNO
L3           0 FILE CONFSCI
L4           0 FILE HEALSAFE
L5           0 FILE IMSDRUGCONF
L6          23 FILE LIFESCI
L7         136 FILE PASCAL

TOTAL FOR ALL FILES
L8         222 ((TISSUE FACTOR) OR THROMBOPLASTIN) AND THROMBOMODULIN AND COAGU
               LATION

=> l8 and concentration and picomolar
L9           0 FILE AGRICOLA
L10          0 FILE BIOTECHNO
L11          0 FILE CONFSCI
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L12           0 FILE HEALSAFE
L13           0 FILE IMSDRUGCONF
L14           0 FILE LIFESCI
L15           0 FILE PASCAL

TOTAL FOR ALL FILES
L16           0 L8 AND CONCENTRATION AND PICOMOLAR

=> l8 and concentration
L17           0 FILE AGRICOLA
L18          23 FILE BIOTECHNO
L19           0 FILE CONFSCI
L20           0 FILE HEALSAFE
L21           0 FILE IMSDRUGCONF
L22           7 FILE LIFESCI
L23          30 FILE PASCAL

TOTAL FOR ALL FILES
L24          60 L8 AND CONCENTRATION

=> dup rem
ENTER L# LIST OR (END):l18
PROCESSING COMPLETED FOR L18
L25          23 DUP REM L18 (0 DUPLICATES REMOVED)

=> l25 and low
L26           0 S L25
L27           0 FILE AGRICOLA
L28          23 S L25
L29           4 FILE BIOTECHNO
L30           0 S L25
L31           0 FILE CONFSCI
L32           0 S L25
L33           0 FILE HEALSAFE
L34           0 S L25
L35           0 FILE IMSDRUGCONF
L36           0 S L25
L37           0 FILE LIFESCI
L38           0 S L25
L39           0 FILE PASCAL

TOTAL FOR ALL FILES
L40           4 L25 AND LOW

=> d l40 ibib abs total

L40   ANSWER 1 OF 4  BIOTECHNO  COPYRIGHT 2007 Elsevier Science B.V. on STN
ACCESSION NUMBER:         2003:36722224   BIOTECHNO
TITLE:                    The coagulation system as a target for
                          experimental therapy of human gliomas
AUTHOR:                   Loynes J.T.; Zacharski L.R.
CORPORATE SOURCE:         Dr. J.T. Loynes, Section of Hematology/Oncology,
                          Dartmouth-Hitchcock Medical Center, One Medical Center
                          Drive, Lebanon, NH 03257, United States.
                          E-mail: James.T.Loynes@Hitchcock.org
SOURCE:                   Expert Opinion on Therapeutic Targets, (2003), 7/3
                          (399-404), 55 reference(s)
                          CODEN: EOTTAO  ISSN: 1472-8222
DOCUMENT TYPE:            Journal; General Review
COUNTRY:                  United Kingdom
LANGUAGE:                 English
SUMMARY LANGUAGE:         English
AN    2003:36722224   BIOTECHNO
AB    The purpose of this paper is to review the rationale for the development
```

of coagulation-reactive drugs for the experimental therapy of gliomas. Numerous reactants familiar to students of blood coagulation have been shown to contribute to neoplastic proliferation, invasion and metastasis. Recently, considerable progress has been made in demonstrating the ability of drugs capable of inhibiting these reactants to alter cancer progression. Biological features of gliomas within the realm of blood coagulation suggest that clinical trials of such drugs warrant consideration. This approach offers the prospect of a novel treatment for this devastating tumour type that does not share the toxicities of conventional cancer therapies.

L40 ANSWER 2 OF 4 BIOTECHNO COPYRIGHT 2007 Elsevier Science B.V. on STN
ACCESSION NUMBER: 2001:32050935 BIOTECHNO
TITLE: Regulation of fibrinolysis in plasma by TAFI and protein C is dependent on the concentration of thrombomodulin
AUTHOR: Mosnier L.O.; Meijers J.C.M.; Bouma B.N.
CORPORATE SOURCE: Dr. L.O. Mosnier, Dept. Haematology (G03.647), University Medical Center Utrecht, P.O. Box 85500, 3508 GA Utrecht, Netherlands.
E-mail: lmosnier@lab.azu.nl
SOURCE: Thrombosis and Haemostasis, (2001), 85/1 (5-11), 48 reference(s)
CODEN: THHADQ ISSN: 0340-6245
DOCUMENT TYPE: Journal; Article
COUNTRY: Germany, Federal Republic of
LANGUAGE: English
SUMMARY LANGUAGE: English
AN 2001:32050935 BIOTECHNO
AB Thrombin activatable fibrinolysis inhibitor (TAFI) is a carboxypeptidase B-like proenzyme, that after activation down regulates fibrinolysis. TAFI is activated by thrombin in the presence of the cofactor thrombomodulin (TM). By stimulation of TAFI activation TM down regulates fibrinolysis, however TM is also a cofactor in the activation of protein C. Activated protein C (APC) can up regulate fibrinolysis by limiting the activation of TAFI via the attenuation of thrombin production. We studied these counteracting fibrinolytic properties of TM in plasma by measuring the activation of TAFI during tissue factor induced coagulation. TAFI activation was stimulated at low concentrations of TM but decreased at higher concentrations of TM. Similarly, the clot lysis times increased at low concentrations of TM but decreased at higher concentrations of TM. The reduction of TAFI activation at high TM concentrations was found to be dependent on a functional protein C pathway. The concentration of TM is therefore an important factor in the regulation of TAFI activation and in the regulation of fibrinolysis. High concentrations of TM result in up regulation of fibrinolysis, whereas low concentrations of TM have a down regulatory effect on fibrinolysis. These results suggest that fibrinolysis might be differentially regulated by TM in different parts of the body depending on the local TM concentration in the vasculature.

L40 ANSWER 3 OF 4 BIOTECHNO COPYRIGHT 2007 Elsevier Science B.V. on STN
ACCESSION NUMBER: 1997:27355637 BIOTECHNO
TITLE: Increased tissue factor-initiated prothrombin activation as a result of the Arg.sup.5.sup.0.sup.6 → Gln mutation in factor V(LEIDEN)
AUTHOR: Van't Veer C.; Kalafatis M.; Bertina R.M.; Simioni P.; Mann K.G.
CORPORATE SOURCE: K.G. Mann, Department of Biochemistry, University of Vermont, Burlington, VT 05405-0068, United States.
SOURCE: Journal of Biological Chemistry, (1997), 272/33

(20721-20729), 42 reference(s)
CODEN: JBCHA3 ISSN: 0021-9258
DOCUMENT TYPE: Journal; Article
COUNTRY: United States
LANGUAGE: English
SUMMARY LANGUAGE: English
AN 1997:27355637 BIOTECHNO
AB The effect of the Arg.sup.5.sup.0.sup.6 → Gln mutation in factor V(LEIDEN) on thrombin generation was evaluated in a reconstituted system using the purified components of the tissue factor (TF) pathway to thrombin and the components of the protein C pathway. Recombinant full-length tissue factor pathway inhibitor (RTFPI) was included in the system because of a previously observed synergistic inhibitory effect of TFPI and the protein C pathway on TF-initiated thrombin generation. Thrombin generation initiated by 1.25 pM factor VIIa-TF in the absence of the protein C pathway components occurs following an initiation phase, after which prothrombin is quantitatively converted to 1.4 μM thrombin. The factor V(LEIDEN) mutation did not influence thrombin generation in the reconstituted model in the absence of the protein C pathway. In the presence of 2.5 nM TFPI, 65 nM protein C, and 10 nM recombinant soluble thrombomodulin (Tm), thrombin generation catalyzed by normal factor V was abolished after the initial formation of 25 nM thrombin. In contrast, persistent thrombin generation was observed in the presence of factor V(LEIDEN) in the same system, although the rate of thrombin generation was slower compared with the reaction without protein C and Tm. The rate of thrombin generation with factor V(LEIDEN) increased with time and ultimately resulted in quantitative prothrombin activation. When the TFPI concentration was reduced to 1.25 nM, thrombin generation is still curtailed in the presence of normal factor V. In contrast, under similar conditions using factor V(LEIDEN), the protein C pathway totally failed to down-regulate thrombin generation. The dramatic effect of a 50% reduction in TFPI concentration on the inhibitory potential of the protein C pathway on thrombin generation catalyzed by factor V(LEIDEN) suggests that the observed synergy between TFPI and the protein C pathway is directly governed by the TFPI concentration and by cleavage of the factor Va heavy chain at Arg.sup.5.sup.0.sup.6. This cleavage appears to have a dramatic regulatory effect in the presence of low concentrations of TFPI. Markedly increased thrombin generation in the presence of both 1.25 nM TFPI and factor V(LEIDEN) was also observed when antithrombin-III was added to the system to complete the natural set of coagulation inhibitors. Protein S (300 nM) had a minimal effect in the model on the inhibition of thrombin generation by protein C, Tm, and TFPI, with either normal factor V or factor V(LEIDEN). Protein S also failed to significantly potentiate the action of the protein C pathway in the presence of antithrombin-III in reactions employing normal factor V or factor V(LEIDEN). The absence of an effect of protein S in the model, which employs saturating concentrations of phospholipid, suggests that the reported interactions of protein S with coagulation factors are not decisive in the reaction. Altogether the data predict that TFPI levels in the lower range of normal values are a risk factor for thrombosis when combined with the Arg.sup.5.sup.0.sup.6 → Gln mutation in factor V(LEIDEN).

L40 ANSWER 4 OF 4 BIOTECHNO COPYRIGHT 2007 Elsevier Science B.V. on STN
ACCESSION NUMBER: 1997:27137362 BIOTECHNO
TITLE: Inhibitory mechanism of the protein C pathway on tissue factor-induced thrombin generation. Synergistic effect in combination with tissue factor pathway inhibitor
AUTHOR: Van't Veer C.; Golden N.J.; Kalafatis M.; Mann K.G.
CORPORATE SOURCE: K.G. Mann, Department of Biochemistry, University of Vermont, Burlington, VT 05405-0068, United States.

SOURCE: Journal of Biological Chemistry, (1997), 272/12 (7983-7994), 60 reference(s)
CODEN: JBCHA3 ISSN: 0021-9258
DOCUMENT TYPE: Journal; Article
COUNTRY: United States
LANGUAGE: English
SUMMARY LANGUAGE: English
AN 1997:27137362 BIOTECHNO
AB The effects of the components of the protein C pathway on thrombin generation were studied in a reconstituted model in which thrombin is generated by factor VIIa and relipidated tissue factor (TF) via the activation of the purified coagulation factors X, IX, VIII, V, and prothrombin. The influence of protein C and soluble thrombomodulin on thrombin generation was correlated with factor Xa generation, factor V(a) and factor VIII(a) formation/inactivation, and protein C activation. Thrombin generation initiated by low concentrations of factor VIIa.midldot.TF (1.25 pM) occurs in an explosive fashion during a propagation phase which occurs after an initiation phase of 1 rain in which only traces of thrombin are formed. In the absence of other inhibitors, protein C (85 nM) in combination with high concentrations of soluble thrombomodulin (10 nM) resulted in a reduced rate of thrombin generation during the propagation phase without affecting the initiation phase; the activated protein C generated failed to neutralize prothrombinase activity and did not prevent prothrombin consumption. In the presence of plasma levels of the tissue factor pathway inhibitor (2.5 nM recombinant TFPI), the protein C pathway reduced the rate of thrombin generation, initiated by 1.25 pM factor VIIa.midldot.TF, and completely eliminated prothrombinase activity at soluble thrombomodulin concentrations of <=1 nM. The neutralization of prothrombinase activity coincided with cleavages at Arg-506 and subsequent cleavage at Arg-306 of the factor Va heavy chain by activated protein C. Thus, the protein C pathway combined with TFPI creates a minimal inhibitory potential required to shut down TF-initiated thrombin generation. The protein C pathway constituents did not influence factor Xa generation or factor VIlla degradation over the interval in which prothrombinase activity was neutralized. Our data thus suggest that the protein C pathway regulates thrombin generation solely by the inactivation of factor Va. At low initiating factor VIIa.midldot.TF (1.25 pM) and high thrombomodulin concentrations (10 nM), the factor Va heavy chain is cleaved before significant amounts of light chain are generated. The ability of the protein C pathway to inhibit thrombin generation was greatly reduced when the reaction was initiated in the presence of factor Va, supporting the hypothesis that effective down-regulation of thrombin generation by the protein C pathway, in reactions initiated with the procofactor, occurs by prevention of the coexistence of the factor Va heavy and light chains.

=> FIL STNGUIDE

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	27.24	27.45

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ENTER A FILE NAME OR (IGNORE):ignore
'MEDICONF' IS NOT A VALID FILE NAME
Enter "HELP FILE NAMES" at an arrow prompt (=>) for a list of files
that are available. If you have requested multiple files, you can
specify a corrected file name or you can enter "IGNORE" to continue
accessing the remaining file names entered.
ENTER A FILE NAME OR (IGNORE):ignore
COST IN U.S. DOLLARS SINCE FILE ENTRY TOTAL SESSION
FULL ESTIMATED COST 0.48 27.93

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=> ((tissue factor) or thromboplastin) and thrombomodulin and coagulation and (picomolar or pM)
L41 0 FILE AGRICOLA
L42 3 FILE BIOTECHNO
L43 0 FILE CONFSCI
L44 0 FILE HEALSAFE
L45 0 FILE IMSDRUGCONF
L46 1 FILE LIFESCI
L47 1 FILE PASCAL

TOTAL FOR ALL FILES
L48 5 ((TISSUE FACTOR) OR THROMBOPLASTIN) AND THROMBOMODULIN AND COAGULATION AND (PICOMOLAR OR PM)

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ANSWERS FROM THESE FILES WILL BE CONSIDERED UNIQUE
PROCESSING COMPLETED FOR L48
L49 4 DUP REM L48 (1 DUPLICATE REMOVED)

=> d l49 ibib abs total

L49 ANSWER 1 OF 4 PASCAL COPYRIGHT 2007 INIST-CNRS. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2005-0146157 PASCAL
TITLE (IN ENGLISH): Inhibition of thrombin generation by protein S at low procoagulant stimuli: implications for maintenance of the hemostatic balance
AUTHOR: SERE Kristin M.; ROSING Jan; HACKENG Tilman M.
CORPORATE SOURCE: Department of Biochemistry, Cardiovascular Research Institute, Maastricht University Maastricht, Maastricht, Netherlands
SOURCE: Blood, (2004), 104(12), 3624-3630, 31 refs.
ISSN: 0006-4971
DOCUMENT TYPE: Journal
BIBLIOGRAPHIC LEVEL: Analytic
COUNTRY: United States
LANGUAGE: English
AVAILABILITY: INIST-3178, 354000126449370290
AN 2005-0146157 PASCAL
AB The activated protein C (APC)-independent anticoagulant activity of protein S on tissue factor-induced thrombin generation was quantified in plasma. In absence of APC, protein S significantly decreased the endogenous thrombin potential (ETP) in a concentration-dependent manner. The APC-lndependent anticoagulant activity of protein S in plasma was not affected by phospholipid concentrations but strongly depended on tissue factor concentrations: protein S inhibited the ETP from 6% at 140 pM tissue factor to 74% at 1.4 pM tissue factor. Plasma with both 60% protein S and 140% prothrombin showed an ETP of 240% compared to normal plasma, suggesting an APC-independent protective role of protein S in the development of thrombosis as a result of protein S deficiency and the prothrombin-G20210A mutation. At high tissue-factor concentrations, protein S hardly expressed APC-independent anticoagulant activity but exerted potent APC-cofactor activity when thrombomodulin or APC were added to plasma. Neutralization of protein S under these conditions resulted in a 20-fold reduction of the anticoagulant activity of APC. The present study shows that protein S effectively regulates coagulation at 2 levels: at low procoagulant stimuli, protein S maintains the hemostatic balance by directly inhibiting thrombin formation, and at high procoagulant stimuli, protein S restores the hemostatic balance via its APC-cofactor activity.

L49 ANSWER 2 OF 4 BIOTECHNO COPYRIGHT 2007 Elsevier Science B.V. on STN DUPLICATE
ACCESSION NUMBER: 1997:27355637 BIOTECHNO
TITLE: Increased tissue factor-initiated prothrombin activation as a result of the Arg.sup.5.sup.0.sup.6 → Gln mutation in factor V(LEIDEN)
AUTHOR: Van't Veer C.; Kalafatis M.; Bertina R.M.; Simioni P.; Mann K.G.
CORPORATE SOURCE: K.G. Mann, Department of Biochemistry, University of Vermont, Burlington, VT 05405-0068, United States.
SOURCE: Journal of Biological Chemistry, (1997), 272/33 (20721-20729), 42 reference(s)
CODEN: JBCHA3 ISSN: 0021-9258
DOCUMENT TYPE: Journal; Article
COUNTRY: United States
LANGUAGE: English
SUMMARY LANGUAGE: English
AN 1997:27355637 BIOTECHNO
AB The effect of the Arg.sup.5.sup.0.sup.6 → Gln mutation in factor V(LEIDEN) on thrombin generation was evaluated in a reconstituted system using the purified components of the tissue factor (TF) pathway to thrombin and the components of the protein C pathway. Recombinant full-length tissue factor pathway

inhibitor (RTFPI) was included in the system because of a previously observed synergistic inhibitory effect of TFPI and the protein C pathway on TF-initiated thrombin generation. Thrombin generation initiated by 1.25 pM factor VIIa-TF in the absence of the protein C pathway components occurs following an initiation phase, after which prothrombin is quantitatively converted to 1.4 μM thrombin. The factor V(LEIDEN) mutation did not influence thrombin generation in the reconstituted model in the absence of the protein C pathway. In the presence of 2.5 nM TFPI, 65 nM protein C, and 10 nM recombinant soluble thrombomodulin (Tm), thrombin generation catalyzed by normal factor V was abolished after the initial formation of 25 nM thrombin. In contrast, persistent thrombin generation was observed in the presence of factor V(LEIDEN) in the same system, although the rate of thrombin generation was slower compared with the reaction without protein C and Tm. The rate of thrombin generation with factor V(LEIDEN) increased with time and ultimately resulted in quantitative prothrombin activation. When the TFPI concentration was reduced to 1.25 nM, thrombin generation is still curtailed in the presence of normal factor V. In contrast, under similar conditions using factor V(LEIDEN), the protein C pathway totally failed to down-regulate thrombin generation. The dramatic effect of a 50% reduction in TFPI concentration on the inhibitory potential of the protein C pathway on thrombin generation catalyzed by factor V(LEIDEN) suggests that the observed synergy between TFPI and the protein C pathway is directly governed by the TFPI concentration and by cleavage of the factor Va heavy chain at Arg.sup.5.sup.0.sup.6. This cleavage appears to have a dramatic regulatory effect in the presence of low concentrations of TFPI. Markedly increased thrombin generation in the presence of both 1.25 nM TFPI and factor V(LEIDEN) was also observed when antithrombin-III was added to the system to complete the natural set of coagulation inhibitors. Protein S (300 nM) had a minimal effect in the model on the inhibition of thrombin generation by protein C, Tm, and TFPI, with either normal factor V or factor V(LEIDEN). Protein S also failed to significantly potentiate the action of the protein C pathway in the presence of antithrombin-III in reactions employing normal factor V or factor V(LEIDEN). The absence of an effect of protein S in the model, which employs saturating concentrations of phospholipid, suggests that the reported interactions of protein S with coagulation factors are not decisive in the reaction. Altogether the data predict that TFPI levels in the lower range of normal values are a risk factor for thrombosis when combined with the Arg.sup.5.sup.0.sup.6 → Gln mutation in factor V(LEIDEN).

L49 ANSWER 3 OF 4 BIOTECHNO COPYRIGHT 2007 Elsevier Science B.V. on STN
ACCESSION NUMBER: 1997:27137362 BIOTECHNO
TITLE: Inhibitory mechanism of the protein C pathway on tissue factor-induced thrombin generation. Synergistic effect in combination with tissue factor pathway inhibitor
AUTHOR: Van't Veer C.; Golden N.J.; Kalafatis M.; Mann K.G.
CORPORATE SOURCE: K.G. Mann, Department of Biochemistry, University of Vermont, Burlington, VT 05405-0068, United States.
SOURCE: Journal of Biological Chemistry, (1997), 272/12 (7983-7994), 60 reference(s)
CODEN: JBCHA3 ISSN: 0021-9258
DOCUMENT TYPE: Journal; Article
COUNTRY: United States
LANGUAGE: English
SUMMARY LANGUAGE: English
AN 1997:27137362 BIOTECHNO
AB The effects of the components of the protein C pathway on thrombin generation were studied in a reconstituted model in which thrombin is generated by factor VIIa and relipidated tissue factor (TF) via the activation of the purified coagulation factors X, IX, VIII, V, and prothrombin. The influence of protein C and soluble

thrombomodulin on thrombin generation was correlated with factor Xa generation, factor V(a) and factor VIII(a) formation/inactivation, and protein C activation. Thrombin generation initiated by low concentrations of factor VIIa.midldot.TF (1.25 pM) occurs in an explosive fashion during a propagation phase which occurs after an initiation phase of 1 rain in which only traces of thrombin are formed. In the absence of other inhibitors, protein C (85 nM) in combination with high concentrations of soluble thrombomodulin (10 nM) resulted in a reduced rate of thrombin generation during the propagation phase without affecting the initiation phase; the activated protein C generated failed to neutralize prothrombinase activity and did not prevent prothrombin consumption. In the presence of plasma levels of the tissue factor pathway inhibitor (2.5 nM recombinant TFPI), the protein C pathway reduced the rate of thrombin generation, initiated by 1.25 pM factor VIIa.midldot.TF, and completely eliminated prothrombinase activity at soluble thrombomodulin concentrations of <=1 nM. The neutralization of prothrombinase activity coincided with cleavages at Arg-506 and subsequent cleavage at Arg-306 of the factor Va heavy chain by activated protein C. Thus, the protein C pathway combined with TFPI creates a minimal inhibitory potential required to shut down TF-initiated thrombin generation. The protein C pathway constituents did not influence factor Xa generation or factor VIlla degradation over the interval in which prothrombinase activity was neutralized. Our data thus suggest that the protein C pathway regulates thrombin generation solely by the inactivation of factor Va. At low initiating factor VIIa.midldot.TF (1.25 pM) and high thrombomodulin concentrations (10 nM), the factor Va heavy chain is cleaved before significant amounts of light chain are generated. The ability of the protein C pathway to inhibit thrombin generation was greatly reduced when the reaction was initiated in the presence of factor Va, supporting the hypothesis that effective down-regulation of thrombin generation by the protein C pathway, in reactions initiated with the procofactor, occurs by prevention of the coexistence of the factor Va heavy and light chains.

L49 ANSWER 4 OF 4 BIOTECHNO COPYRIGHT 2007 Elsevier Science B.V. on STN
ACCESSION NUMBER: 1991:21064663 BIOTECHNO
TITLE: Heterogeneous regulation of constitutive thrombomodulin or inducible tissue-factor activities on the surface of human saphenous-vein endothelial cells in culture following stimulation by interleukin-1, tumour necrosis factor, thrombin or phorbol ester
AUTHOR: Archipoff G.; Beretz A.; Freyssinet J.-M.; Klein-Soyer C.; Brisson C.; Cazenave J.-P.
CORPORATE SOURCE: INSERM U.311, Centre Regional, de Transfusion Sanguine, 10 Rue Spielmann,67085 Strasbourg, France.
SOURCE: Biochemical Journal, (1991), 273/3 (679-684)
CODEN: BIJOAK ISSN: 0264-6021
DOCUMENT TYPE: Journal; Article
COUNTRY: United Kingdom
LANGUAGE: English
SUMMARY LANGUAGE: English
AN 1991:21064663 BIOTECHNO
AB Thrombomodulin and tissue-factor activities were measured on the surface of confluent human saphenous-vein endothelial cells (HSVEC) cultivated in 96-multiwell plates. Thrombomodulin activity was measured in the presence of purified human thrombin (2.2 nM) and protein C (65 nM). Tissue-factor activity was measured with purified human Factor VII (5 nM) and Factor X (400 nM). Generated activated protein C and Factor Xa released in the supernatant were assayed with chromogenic substrates. Resting cells exhibited significant thrombomodulin activity, but no detectable tissue factor activity. After 4 h

of preincubation with tumour necrosis factor (TNF, 22-2200 pM), interleukin-1 (IL-1, 5.7-570 nM) or phorbol myristate acetate (PMA, 1.61-161 nM) there was an increase in tissue-factor activity and a concomitant decrease in thrombomodulin activity. However, the extent of both responses varied according to the nature of the stimulus. Thrombin (0.44-44 nM) also induced an increase in tissue-factor activity, but had no effect on thrombomodulin activity. Kinetic studies showed that for all stimuli the increase in tissue factor was transient, reaching a maximum after 4-8 h of preincubation with the stimulating agent and returning to normal values after 24 h. IL-1 and TNF induced a time-dependent decrease in thrombomodulin, by respectively 47% and 67% of control values after 24 h. However, PMA induced only a transient down-regulation of thrombomodulin, full activity being recovered after 18 h. Hence this simultaneous assay system, using intact HSVEC and purified human coagulation factors, enabled us to observe that the regulation of thrombin generation could be diversely affected by various substances known to stimulate the endothelium. This suggests that the simultaneous and opposite modulation of these proteins does not represent an unified response of the endothelial cells to procoagulant stimuli. These results also confirm the absence of effect of thrombin on the expression of thrombomodulin on the cell surface.